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(Cite as: Not Reported in F.Supp.)

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United States District Court, D. Delaware.
AJINOMOTO CO., INC., Plaintiff,
v.
ARCHER-DANIELS-MIDLAND CO., Defendant.
No. 95-218-SLR.

March 13, 1998.

Edward M. McNally, and Peter A. Pietra, of Morris, James, Hitchens & Williams, Wilmington, Delaware, of counsel Arthur I. Neustadt, Marc R. Labgold, William J. Healey, and Catherine B. Richardson, of Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Arlington, VA, Thomas Field, and Lawrence Rosenthal, of Strook & Strook & Lavan, New York City, for plaintiff.
Jack B. Blumenfeld, and Thomas C. Grimm, of Morris, Nichols, Arsht & Tunnell, Wilmington, Delaware, of counsel Charles A. Laff, John T. Gabrielides, Kevin C. Trock, of Laff, Whitesel, Conte & Saret, Ltd., Chicago, Illinois, J. Alan Galbraith, and Ari S. Zymelman, of Williams & Connolly, Washington, D.C., for defendant.

OPINION

ROBINSON, J.

I. INTRODUCTION

*1 Plaintiff Ajinomoto Co., Inc. ("Ajinomoto") filed this suit pursuant to 35 U.S.C. § 271(g) against defendant Archer-Daniels-Midland Co. ("ADM") on April 6, 1995 seeking damages (lost royalty income) and an injunction against defendant Archer-Daniels-Midland ("ADM") for alleged infringement of a patent that is directed to a method for the preparation of bacterial strains possessing enhanced capability of producing amino acids.

Specifically, Ajinomoto charges that ADM willfully infringed claims 1 and 2 of U.S. Patent No. 4,278,765 ("the '765 patent") entitled "Method for Preparing Bacterial Strains Which Produce Amino Acids" issued on July 14, 1981. The priority patent to this patent was filed in the former Soviet Union on June 30, 1978.

Defendant denies infringement and challenges the validity and enforceability of the '765 patent under 35 U.S.C. § § 112 ("obviousness"), 103 ("best mode" and "enablement"), and 115 and 116 ("oath of applicant"). Specifically, ADM charges that: (1) the specification of the '765 patent: (a) does not disclose the best mode contemplated by the inventors of carrying out their invention, (b) fails to enable the full scope of generic claims 1 and 2 without undue experimentation, and (c) lacks the deposit of the biological materials in a depository that will distribute samples of the material to members of the public who wish to practice the invention after the patent issues (§ 112); (2) the differences between the patented invention and the prior art are such that claims 1 and 2 would have been obvious to one of ordinary skill in the pertinent art (§ 103); and (3) not all of the inventors personally signed the declarations required to grant the '765 patent (§ § 115, 116). Additionally, ADM contends that Ajinomoto lacks standing to sue ADM for infringement of the '765 patent because the chain of title of the '765 patent from the named inventors to Ajinomoto was not established. Moreover, ADM affirmatively defends that the '765 patent is invalid because the patent applicants conducted themselves inequitably in their prosecution of the patent application by withholding and concealing prior art and by concealing the best mode of carrying out the invention.

The court has jurisdiction over this matter pursuant to 28 U.S.C. § 1338(a).

The parties tried this matter to the court from October 28, 1996 through November 11, 1996. The following constitutes the court's findings of fact and conclusions of law pursuant to Fed.R.Civ.P. 52(a).

II. FINDINGS OF FACT

A. The Invention

1. **Amino Acids.** The '765 patent is directed to a method for the construction of genetically engineered bacterial strains possessing an enhanced capability of producing selected amino acids, such as threonine, without the need for additional growth factors. (Joint Exhibit ("JX") 1 at col. 3, lines 1-4) Amino acids are the building blocks of proteins. Proteins are

complex macromolecules composed of long chains of amino acids that carry out structural and/or catalytic functions in cells. (D.I. 307 at 97-99) There are twenty amino acids: alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, aspartic acid, glutamic acid, lysine, arginine, and histidine.

***2** 2. The '765 patent specifically discloses a method for producing an Escherichia coli ("E.coli") bacteria capable of overproducing the amino acid threonine. (JX 1) Threonine is of great industrial importance. It is an essential amino acid which, because it cannot be produced by any animal, must be supplied through dietary supplements. ADM's animal feed supplements supply various essential amino acids, including threonine.

3. A bacterial strain is a type or variety of a particular species of bacteria. There are thousands of known species of bacteria, as well as many bacterial strains within each species. All bacteria naturally make amino acids. Bacterial strains prepared in accordance with the patented technology can reduce the cost of producing amino acids, which are used, *inter alia,* as feedstuff and food additives in the agriculture and food industry. (JX 1 at col. 1, lines 8-12)

4. **Threonine Biosynthesis.** Threonine synthesis in a cell is a five step process. (Docket Item ("D.I.") 308 at 322-24; D.I. 313 at 941; Defendant's Exhibit ("DX") 298 at 346; DX 1005) In step 1, aspartate is converted into aspartyl phosphate. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) Step 2 involves the conversion of aspartyl phosphate into aspartate semialdehyde. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) The third step involves the conversion of aspartate semialdehyde into homoserine. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) In step 4, homoserine is converted into O-phospho homoserine. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) And finally, in step 5, O-phospho homoserine is converted into threonine. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) Subsequently, some of the threonine is converted into isoleucine; the product of the *ilvA* gene catalyzes the first step in this transformation. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) Through separate pathways, the process also results in the synthesis of lysine and methionine from the threonine precursors aspartate semialdehyde and homoserine, respectively. (D.I. 313 at 940-43; DX 298 at 346; DX 1005)

5. In E. coli[FN1] the entire process is catalyzed by a variety of enzymes,[FN2] three of which are coded by the threonine operon.[FN3] (D.I. 307 at 105-06; D.I. 313 at 947; DX 298 at 346; DX 1005) The threonine operon contains three structural genes: *thrA, thrB,* and *thrC.* (D.I. 307 at 105-06; D.I. 313 at 947; DX 298 at 346; DX 1005) The *thrA* gene codes for a bifunctional enzyme-aspartokinase for *thrA* 1 and homoserine dehydrogenase for *thrA* 2-which catalyze steps 1 and 3, respectively. (D.I. 307 at 105-06; D.I. 313 at 940-43; DX 298 at 346; DX 1005) The two remaining genes, *thrB* and *thrC,* code for homoserine kinase (step 4) and threonine synthetase (step 5), respectively. (D.I. 307 at 105-06; D.I. 313 at 940-43; DX 298 at 346; DX 1005)

FN1. The biosynthetic pathway for the production of threonine is not the same in all bacterial species. (D.I. 307 at 944-946) For example, with respect to *Corynebacteria,* although the basic steps in the pathway are the same, the number of isoenzymes involved in the various steps varies as does the method of regulation. (D.I. 313 at 944-46) In addition, in *Corynebacteria* although the *thrA* and *asd* genes are together on one part of the bacterial chromosome, the *thrB* and *thrC* are on two separate pieces of DNA. (D.I. 313 at 944-46)

FN2. The first step is catalyzed by three isoenzymes, the second by one, the third by two, the fourth by one, and the fifth by one. (D.I. 313 at 941) An isoenzyme (or isozyme) is one of a group of enzymes that are very similar in catalytic properties, but can be distinguished based on variations in physical properties.

FN3. The term operon is defined as "[a] unit of genetic expression consisting of one or more related genes and the operator and promotor sequences that regulate their transcription." Albert L. Lehninger, *Principles of Biochemistry* 977 (Sally Anderson & June Fox eds., 1982). In the '765 patent, the term operon is defined as "a jointly controlled group of genes generally monitoring the synthesis of a single product, e.g. aminoacid." (JX 1 at col. 1, lines 49-51)

6. The product of the *asd* gene,[FN4] which is located outside of the threonine operon (approximately 1500 genes away), catalyzes the conversion of aspartyl

phosphate into the semialdehyde of aspartic acid (the second step in threonine synthesis). (D.I. 313 at 947) This is not a limiting step in the biosynthetic process.

FN4. Although Ajinomoto asserts that testimony regarding the role of the *asd* gene in the biosynthesis of threonine should be discarded because of insufficient notice, the issue was raised by Ajinomoto's expert witness, Dr. Joseph O. Falkinham III, on cross-examination when he was questioned regarding threonine synthesis in E. coli.

***3** 7. In E. coli, regulation of the threonine operon is accomplished by means of a multivariant repression mechanism (negative feedback regulation), so that when a large amount of a particular product is formed, it blocks its own synthesis. (D.I. 313 at 942) With respect to the first step of threonine synthesis, lysine inhibits one of the isozymes, methionine inhibits a second isozyme, and isoleucine and threonine inhibit the third isozyme. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) Lysine and methionine also regulate their own synthesis. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) In addition, threonine and isoleucine inhibit one of the isozymes involved in step 3. (D.I. 313 at 940-43; DX 298 at 346; DX 1005) Besides the feedback inhibition effect that changes the activity of the level of the available enzyme, isoleucine and threonine also affect the level of available enzyme-as the levels of isoleucine and threonine increase, the amount of enzyme decreases. (D.I. 313 at 940-43)

8. **The Technology Developed by the Genetika Researchers.** The method of preparation set forth in the '765 patent was developed by fourteen researchers at the Institute for Genetic Engineering and Industrial Microbiology ("Genetika") in the former Soviet Union. (D.I. 307 at 123-24) In developing the process, the researchers combined skills from both classical genetics and recombinant DNA technology. (D.I. 307 at 126) Although not the first scientists to employ recombinant DNA technology, the Genetika researchers were the first in the former Soviet Union to do so. (DX 1100 at 30-31) Unlike their peers in other countries who were applying recombinant DNA technology [FN5] to the development of pharmaceuticals, the Genetika researchers applied this technology to the production of enzymes and, as in the case of the '765 patent, amino acids. (D.I. 307 at 124-26)

FN5. Herb Boyer and Stanley Cohen of Stanford University and the University of California, San Francisco respectively developed recombinant DNA technology. (D.I. 307 at 111) The technology was first described in a paper in The Proceedings of the National Academy of Sciences in November 1973. (D.I. 307 at 111) As compared to classical genetics, which typically involves exposing microorganisms to mutagens that randomly alter genetic material and then screening for mutants with desired characteristics, recombinant DNA technology involves the making of specific alterations in DNA, generally through the cutting and then ligating of DNA from different sources. (D.I. 307 at 111)

9. In order to create a bacterial strain capable of overproducing threonine, the Genetika researchers used a strain of E. coli that was feedback resistant for the amino acid threonine. (JX 1 at col. 3, lines 30-36) Using recombinant DNA technology,[FN6] the researchers isolated the threonine operon from the strain and combined this chromosomal fragment with a plasmid. [FN7] (JX 1 at col. 3, lines 30-36) This hybrid plasmid was then inserted into a host bacterial strain that was auxotrophic [FN8] with respect to threonine and contained a partial block ("leaky auxotroph") in the related step of metabolism, the conversion of threonine to isoleucine. (JX 1 at col. 3, lines 46-51) The resultant strain of bacteria was capable of the over production of threonine.

FN6. For basic background information about molecular biology and recombinant DNA technology, see *In re O'Farrell*, 853 F.2d 894, 895-99 (Fed.Cir.1988).

FN7. The term plasmid refers to "[a]n extrachromosomal, independently replicating small circular DNA molecule." Albert L. Lehninger, *Principles of Biochemistry* 977 (Sally Anderson & June Fox eds., 1982).

FN8. An auxotrophic bacterial strain possesses a mutation that renders it "defective in the synthesis of a given biomolecule, which must thus be supplied for its normal growth." *Principles of Biochemistry* 970 (Sally Anderson & June Fox eds., 1982).

B. The '765 Patent Application

10. **The Russian Patent Application.** On June 30, 1978, fourteen Genetika researchers [FN9] filed a Russian patent application entitled "Method for Preparing Strains Producing Aminoacids" (application no. 2639616) ("the Russian patent application"). (Plaintiff's Exhibit ("PX") 2) This patent was directed to "a method for preparing strains of microorganisms possessing an increased ability of producing aminoacids [sic] and lack of demands for additional growth factors." (PX 2 at 80) According to Soviet law, the Russian patent application was personally signed by all fourteen inventors. (D.I. 196 at Ex. 5, ¶ 44)

FN9. The fourteen inventors were: Vladimir G. Debabov, Jury I. Kozlov, Nelli I. Zhdanova, Evgeny M. Khurges, Nikolai K. Yankovsky, Mikhail N. Rozinov, Rustem S. Shakulov, Boris A. Rebentish, Vitaly A. Livshits, Mikhail M. Gusyatiner, Sergei V. Mashko, Vera N. Moshentseva, Ljudmila F. Kozyreva, and Raisa A. Arsatiants.

*4 The Russian patent application listed sixteen references, the pertinent contents of which were identified by use of reference numbers throughout the text of the specification. (PX 2 at 98) Of these references, only the following are relevant to the case at bar: (1) an article authored by several of the named co-inventors of the '765 patent (Gusyatiner, Zhdanova, Livshit [[[[s]; and Shakulov) entitled *Investigation of the function of the relA gene in the expression of amino acid operons: Communication II. Influence of the allelic state of the relA gene on oversynthesis of threonine by a mutant of Escherichia coli K-12 resistant to beta-hydroxynorvaline* appearing in the publication Genetika 14(6) (June 1978) ("Genetika II") and (2) an article entitled *A Suitable Method for Construction and Molecular Cloning Hybrid Plasmids Containing EcoRI-fragments of E. coli Genome* authored by Kozlov et al. (including the named co-inventors Kozlov, Rebentish, and Debabov) published in Molecular and General Genetics in 1977 ("the Kozlov article").

11. **U.S. Patent Application.** The same fourteen inventors who filed the Russian patent application filed the United States counterpart to the Russian patent application on June 28, 1979, two days before the end of the one year priority period.[FN10] (PX 2) The inventors claimed a priority filing date of June 30, 1978 based upon the Russian application. (PX 2) The following documents were included along with the U.S. patent application: (1) a Russian Language Declaration for Original Patent Application ("Russian Language Declaration"); (2) the original Russian patent application; and (3) an English translation of the Russian patent application. (PX 2)

FN10. Title 35 U.S.C. § 119 provides a right of priority for U.S. patent applications if an application for a patent on the same invention was previously filed in a foreign country. Section 119 provides, in part:
An application for patent for an invention filed in this country ... shall have the same effect as the same application would have if filed in this country on the date on which the application for patent ... was first filed in such foreign country, **if the application in this country is filed within twelve months** from the earliest date on which such foreign application was filed; but **no patent shall be granted on any application for patent for an invention which had been patented ... in any country more than one year** before the date of the actual filing of the application in this country....
35 U.S.C. § 119 (emphasis added).

12. **The Inventors' Signatures.** The Russian Language Declaration and the Russian patent application contain fourteen signatures purporting to be the signatures of the fourteen original inventors. (PX 2 at 48-53) With respect to the Russian Language Declaration, each signature is followed by a typed date of June 21, 1979. (PX 2 at 48-53) Dr. Juri Ivanovich Kozlov [FN11] testified that the signature on the Russian Language Declaration is not his own; however, the signor, who he believed to be an employee in Genetika's patent department, "had [his] permission to put [his] signature in [his] absence." (DX 1106 at 144) Dr. Kozlov further testified that he did not remember if he read the declaration or whether it was explained to him before he granted permission for someone to sign it for him. (DX 1106 at 145-46)

FN11. Only two of the original fourteen inventors were deposed in this litigation. None of the inventors testified at trial.

13. Dr. Vladimir Georgievich Debabov testified that his signature on the Russian Language Declaration is, in fact, his own. (DX 1100 at 42) Although he does

not remember the date on which he signed the declaration, he believed it must have been June 21, 1979 since that is the date on the form. (DX 1100 at 42)

14. **The Prior Art References.** The U.S. patent application omitted the sixteen references found in the Russian patent application. However, unlike the Russian patent application, the U.S. patent application cited six publications which described in detail the method of *in vitro* preparation of hybrid DNA molecules and the introduction of these molecules into a recipient strain by means of transformation or transfection using a plasmid or bacteriophage as a vector. (JX 1 at col. 2, lines 37-44) Of these publications two are relevant to the case at bar: (1) an article authored by Clarke and Carbon entitled *Biochemical Construction and Selection of Hybrid Plasmids Containing Specific Segments of the Escherichia coli Genome,* which was published in Proc. Nat'l Acad. Sci. USA, Vol. 72, No. 11 in November 1975 ("the Clarke/Carbon article") and (2) the Kozlov article. (JX 1 at col. 2, lines 52-53, 56-58)

***5** 15. At the time the '765 patent application was submitted, applicants were encouraged to file a prior art statement listing therein, "in the opinion of the person filing[,] ... the closest prior art of which that person is aware." 37 C.F.R. § 1.97(a)-(b) (1978). Said statement was "not to be construed as a representation that a search ha[d] been made or that no better art exist[ed]." 37 C.F.R. § 1.37(b). The statement was to be accompanied by a copy of each listed patent or publication. 37 C.F.R. § 1.98(a). A prior art statement was not submitted as part of the '765 patent application.

According to ADM's expert in Patent and Trademark Office ("PTO") procedure, Mr. Van Horn, at the time of the invention, a PTO Examiner was not likely to review publications that were merely mentioned in the patent application. (D.I. 316 at 1420) Moreover, he testified that unless circumstances arose that necessitated an Examiner to review a priority patent application (e.g., a challenge to the priority date), the content of a priority patent was not reviewed as part of a normal examination of a patent application. (D .I. 316 at 1427-28; DX 268 at 28) If an applicant wanted to be assured that the Examiner considered certain information, he could submit copies of publications or other information to the PTO. (D.I. 316 at 1421) Mr. Van Horn also testified that there were two ways for an Examiner to indicate that a particular reference had been considered: (1) citing the documents in the patent application or (2) placing his initials next to the citation with an indication that it had been checked. (D.I. 316 at 1423-24) The record indicates that neither method was employed with respect to the '765 patent.

16. The American attorneys who prosecuted the '765 patent did not recall providing the PTO Examiner with copies of Genetika II, the Clarke/Carbon article, or the Kozlov article. (DX 1101 at 44-45; DX 1119 at 28, 32-33) The attorneys testified that their standard procedure with respect to patent applications filed on behalf of Genetika was to check the application for compliance with PTO guidelines and to submit the application basically as is, i.e., without supplementation. (DX 1101 at 40-44; DX 1107 at 28-29, 49-52; DX 1119 at 45-49) It is undisputed that the applicants had knowledge of the existence of the aforementioned articles. It is also undisputed that the Clarke/Carbon article and the Kozlov article are material.

17. **U.S. Patent Prosecution History.** On January 21, 1980, during the prosecution of the '765 patent application, the PTO Examiner rejected claims 1-4 as not enabled under 35 U.S.C. § 112. (PX 2 at 100) In an Office Action dated January 21, 1980, the Examiner cited the following reasons for his rejection of the claims:

(1) Applicants fail[ed] to comply with requirements (1) and (3) of MPEP 608.01(p) Deposit of Microorganisms [FN12] regarding the parent E. coli strains and the newly produced E. coli strains.[FN13]

FN12. At the time the application for the '765 patent was pending, § 608.01(p) of the Manual of Patent Examining Procedure ("MPEP") provided as follows:

> Some inventions which are the subject of patent applications depend on the use of microorganisms which must be described in the specification in accordance with 35 U.S.C. 112. No problem exists when the microorganisms used are known and readily available to the public. When the invention depends on the use of a microorganism which is not so known and readily available, applicants must take additional steps to comply with the requirements of Section 112.
>
> In the latter circumstances, the MPEP required applicants to make "a deposit of a culture of the microorganism in a depository

affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted...." The section further provided that "all restrictions on the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent." (D.I. 64, Ex C)

FN13. According to the specification, two of the strains, VL334(pYN6) and VL334(pYN7) having registration numbers CMIM B-1649 and CMIM B-1684, respectively, already were deposited in the Central Museum of Industrial Microorganisms of the All-Union Research Institute of Industrial Microorganisms ("the Central Museum") at the time the application was filed. (PX 2 at 21-22)

*6 (2) Claims are improper process claims in failing to affirmatively recite steps.
(3) The disclosure is not enabling to support the breadth of the terms "vector DNA molecule." Only plasmids appear to be suitable and operative as the vector.

(PX 2 at 100) The Examiner went on to state that "[t]he listed references [[[[were] considered to be pertinent to the claimed invention, but the claims are deemed patentable thereover." FN14

FN14. Two references were cited on Form PTP-892, Notice of References Cited: Sinsheimer, *Ann.Rev. Biochem* 46, 415-438, 1977 and Itokura et al., *Science* vol. 98, pp. 1056-1063. (PX 2 at 101) A copy of the Sinsheimer reference was included in the file wrapper. (PX 2 at 142-164)

18. In May 1980, in response to the Examiner's rejection, the one of the applicants' attorneys, Charles Rodman, agreed to "attempt to rectify depository deficiencies" by "furnishing a new declaration containing the required information." (PX 2 at 103, 119) In addition, Mr. Rodman agreed to "amend [[[[the] claims extensively to eliminate [§] 112 rejections." (PX 2 at 103)

19. On May 21, 1980, Mr. Rodman filed a response to the Office Action requesting reconsideration of the application and entry of numerous amendments, consisting mainly of editorial and typographical corrections in accordance with the PTO action. (PX 2 at 119) He also added the following to the patent application: "The parent strains of VNIIGenetika MG442 and VNIIGenetika VL334 are also deposited in the aforesaid Central Museum and are identified by the registration numbers CMIM B-1641 and CMIM B-1628, respectively." Mr. Rodman stated that he was in the "process of obtaining a Supplementary Declaration from the inventors containing the depository identification of the parent strains and the product strains." He added that he "considered the references cited by the Examiner to show the state of the art, however, inasmuch as these references have not been cited against the claims, and do not appear relevant thereto, a detailed discussion of them shall not appear herein." (PX 2 at 121) A supplemental response to the January 21, 1980 Office Action was filed in August 1980. (PX 2 at 122-24)

20. On August 25, 1980, Mr. Rodman filed the Supplemental Combined Declaration and Power of Attorney ("Supplemental Declaration of 1980") (PX 2 at 125-129) with the PTO, representing under penalty of perjury that,
no later than the effective U.S. filing date of the application, [they had] made a deposit of a culture of the microorganism in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted, under conditions which assure (a) that access to the culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. § 122, and (b) that all restrictions on the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent.
This deposit is identified by: Deposit number CMIM B-1628, CMIM B-1641, CMIM B-1649, CMIM B-1684.
Name and address of the depository: Central Museum of Industrial Microorganisms of the All-Union Research Institute of Genetics and Selection of Industrial Microorganisms, USSR, Moscow 113545, Dorozhnaya S.
*7 Taxonomic description (if available): Escherichia coli K-12.

(PX 2 at 126) The donor strain (MG442) was registered as CMIM B-1628; the recipient strain (VL334) was registered as CMIM B-1641; the product of claim 3 (VL334(pYN6)) was registered as CMIM B-1649; and the product of claim 4 (VL334(pYN7)) was registered as CMIM B-1684. (PX 2 at 126) The filing of the Supplemental Declaration of 1980 overcame the Examiner's § 112 rejection of the claims by representing that the strains

had been deposited.

21. **The Inventors' Signatures.** The Supplemental Declaration of 1980 contains fourteen signatures, all dated July 17, 1980, that purport to be the signatures of the fourteen original inventors. (PX 2 at 127-29) However, Dr. Kozlov testified that the Kozlov signature is not his own, and that he was unaware of who signed. (DX 1106 at 146-47) Nevertheless, Kozlov testified that he knew of and authorized the signing of his name to the Supplemental Declaration of 1980 but that he was unsure of the date of the signing. (DX 1106 at 146-47) The Kozlov signature on the Supplemental Declaration is consistent in appearance with the Kozlov signature on the Russian Language Declaration. (D.I. 314 at 1256, 1258-59; DX 149; DX 390; DX 1106 at 1104) Dr. Kozlov further testified that he did not remember if he read the Supplemental Declaration of 1980 or if it was explained to him before he authorized someone to sign for him. (DX 1106 at 145-46)

Dr. Debabov testified that he personally signed the Supplemental Declaration of 1980 but that someone else wrote the date next to his signature. (DX 1100 at 44-45) Dr. Debabov further testified that he did not read the Supplemental Declaration of 1980 because it was explained to him by someone in the patent department. (DX 1100 at 115-17)

22. The PTO Examiner subsequently issued a Notice of Allowance (PX 2 at 133) and the '765 patent issued on July 14, 1981.

23. In order to rectify the signature discrepancies, on August 5, 1996, Ajinomoto filed with the PTO a Supplemental Declaration ("Supplemental Declaration of 1996") that contains the true signatures, according to counsel for Genetika, Mr. Mtibelishvili, of the fourteen inventors along with a petition to the Commissioner of Patents and Trademarks pursuant to 37 C.F.R. § § 1.67 and 1.182 requesting that the PTO place the Supplemental Declaration of 1996 in the file wrapper. (PX 900) Ajinomoto claimed that the filing containing the authorized signatures "was the result of a lack of knowledge of the technical requirements of U.S. patent law and was made without any deceptive intent." (PX 900)

24. ADM' expert witness, Mr. Lyndal L. Shaneyfelt, a retired FBI document examiner, compared the fourteen signatures on the Russian Language Declaration to the fourteen signatures on the Supplemental Declaration of 1980 and found that six (and possibly seven) of the signatures were not written by the same person. (D.I. 314 at 1247) However, Mr. Shaneyfelt conceded that the signatures were difficult to compare since those on the Russian Language Declaration were written using the Russian alphabet, whereas those on the Supplemental Declaration of 1980 were written using the Arabic alphabet. (D.I. 314 at 1246) Mr. Shaneyfelt also testified that a comparison of the English signatures on the Supplemental Declaration of 1980 revealed numerous significant writing features in common. (D .I. 314 at 1248-50) He concluded that the at least three, and possibly five, of the signatures were written by the person who made the Debabov signature. (D.I. 314 at 1252) However, he found the examination problematic because there were not "a lot of the same letters." (D.I. 314 at 1251)

***8** Mr. Shaneyfelt also testified that the Kozlov signature on the Russian Language Declaration (DX 390) was "generally consistent" with the exemplar (DX 149) that was done at Dr. Kozlov's deposition in the summer of 1996. (D.I. 314 at 1258) In addition, Mr. Shaneyfelt testified that, after comparing the Kozlov signatures on the Russian Language Declaration and the Supplemental Declaration of 1980 with the Kozlov signature on the Supplemental Declaration of 1996, he was "not able to make [a] determination" that the Kozlov signature was or was not Mr. Kozlov's personal signature because there were "too many inconsistencies." (D.I. 314 at 1258)

According to Mr. Van Horn, if a foreign company owns the patent application, it is appropriate for a representative of the company to sign the declaration as representative of the owner of the application if he has authority and that authority is clearly indicated. (D.I. 316 at 1454) Thus, there is no requirement that the inventors personally sign the declaration. (D.I. 316 at 1454)

C. The '765 Patent

25. The abstract described the invention claimed in the '765 patent as follows:
A method for constructing strains which produce aminoacids [sic] comprising combining of a DNA chromosome fragment of a donor microorganism containing genes controlling the synthesis of a selected aminoacid and having a mutation destroying the negative regulation of the synthesis of this aminoacid with a vector DNA molecule to form a hybrid DNA molecule. Use is made of a vector

DNA molecule capable of providing amplification of the hybrid DNA molecule. The resulting hybrid DNA molecule is used for transforming cells of the recipient strain having the mutation blocking the synthesis of the selected aminoacid in this strain and the mutation partly blocking the related step of metabolism of this aminoacid to yield the strain capable of increased productivity of the selected aminoacid.

(JX 1 at 1)

26. The specification included the following object of the invention claimed:
to use genetic engineering techniques to prepare strains which produce aminoacids [sic] possessing enhanced capability of producing aminoacids without additional growth factors.

(JX 1 at col. 3, lines 1-4)

27. The '765 patent contains five claims. Claims 1 and 2 are generic claims, drawn to a method of producing a microorganism capable of producing any amino acid. Claims 3 and 4 are specifically drawn to methods of producing strains capable of producing threonine. Claim 1 is the only independent claim; claims 2-4 depend on claim 1. Only claims 1 and 2 are in dispute in this case.

28. Claim 1 reads:
1. A method for preparing bacterial strains which produce aminoacids [sic] comprising combining a chromosome DNA fragment of a donor bacterium containing genes controlling the synthesis of a selected aminoacid and having a mutation which destroys the negative regulation of the synthesis of said aminoacid, with a plasmid DNA molecule capable of ensuring amplification, to form a hybrid DNA molecule; transforming with said hybrid DNA molecule, cells of a recipient bacterial strain having a mutation blocking the synthesis of the selected aminoacid in said strain and a mutation partly blocking the related step of metabolism of said aminoacid, to yield a bacterial strain possessing increased productivity of the selected aminoacid.

*9 (JX 1 at col. 12, lines 2-15)

29. Claim 2 provides:
2. A method as claimed in claim 1, wherein for the removal of ballast genetic material, the hybrid DNA molecule is treated, prior to transforming cells of the recipient strain, with specific endonucleases ensuring cleavage of the hybrid molecule of DNA in predetermined sites of the molecule, followed by recombination and joining of the required DNA fragments with polynucleotide ligase.

(JX 1 at col. 12, lines 16-23)

30. Claim 1 of the '765 patent sets forth the steps for producing genetically engineered bacterial strains which produce amino acids. It teaches a two-step process of combining and transforming. First, a chromosome DNA fragment of a donor bacterial strain is combined with a plasmid DNA molecule capable of ensuring amplification to form a hybrid DNA molecule. The piece of chromosomal DNA from the donor bacterial strain, which is part of the hybrid DNA molecule, has two characteristics: (1) it contains the instruction (or genes) for the production of the selected amino acid and (2) it has a mutation blocking the negative regulation of the synthesis of the amino acid (i.e., feedback inhibition resistance has been destroyed) .[FN15] Second, this hybrid DNA molecule is then transformed (or inserted) into a recipient bacterial strain. The recipient bacterial strain must have: (1) a mutation blocking the synthesis of the selected amino acid; and (2) a mutation partly blocking a related step of the metabolism of the selected amino acid. The resulting combination of the hybrid DNA molecule and the recipient bacterial strain has increased production capability of the selected amino acid. The process taught in claim 1 utilizes three major components: (1) a chromosome DNA fragment from a donor bacterial strain; (2) a plasmid DNA molecule; and (3) host cells as the DNA recipient.

FN15. The patent specification first described several experiments using E. coli in which the inventors used an unmutated donor chromosome DNA molecule in combination with a plasmid to form a hybrid DNA molecule. (JX 1 at col. 6, lines 4-22) In these experiments, threonine production did not increase. The specification then set forth Examples 1 and 2, describing the use of a mutated donor chromosome DNA molecule in combination with a plasmid to form a hybrid DNA molecule where threonine production increased. (JX 1 at col. 8, line 45 through col. 10, line 53) In Example 3, the amount of threonine formed by the E. coli strains of Examples 1 and 2 is measured. (JX 1 at col. 10, line 55 through col. 11, line 68)

31. Claim 2 depends from claim 1 and therefore includes all its limitations. It is directed to a method for removing ballast genetic material from the hybrid DNA molecule before its insertion into the recipient strain. Ballast genetic material is unneeded, unwanted DNA. (D.I. 307 at 166; D.I. 313 at 967) In the method of claim 2, prior to transformation, the hybrid DNA molecule is treated with specific endonucleases (restriction enzymes) at predetermined sites (restriction sites) to provide a mixture of DNA fragments, after which the DNA fragments are recombined (ligated) using the enzyme polynucleotide ligase.

D. The Prior Art

32. The publications characterized by ADM as prior art include: (1) a doctoral thesis authored by David Tribe in December 1976 entitled *Tryptophan Production by Escherichia coli: A Feasibility Study,* ("the Tribe thesis") (DX 383); (2) the Kozlov article (DX 321); (3) two articles [FN16] authored by several of the named co-inventors of the '765 patent (Livshits, Shakulov, Gusyatiner, and Zhdanova) appearing in the publication Genetica 14(6) (June 1978) (collectively the "Genetica articles") (DX 305; DX 326); and (4) the Clarke/Carbon article (DX 290). All of these references are within the field of microbial genetics.

FN16. The articles are entitled, respectively, *Investigation of the Allelic State of the relA Gene on the Phenotypic Expression of Mutations of Threonine and Isoleucine Auxotrophy: Communication I. Influence of the allelic state of the relA gene on Phenotypic expression of mutations of threonine and isoleucine auxotrophy in Escherichia coli K-12* ("Genetika I"); and *Investigation of the function of the relA gene in the expression of amino acid operons: Communication II. Influence of the allelic state of the relA gene on oversynthesis of threonine by a mutant of Escherichia coli K-12 resistant to beta-hydroxynorvaline* ("Genetika II").

***10** It is undisputed that none of the prior art publications, standing alone, anticipates the teachings of the '765 patent.

33. **The Tribe Thesis: Availability.** ADM relies entirely upon the testimony of Dr. Tribe to establish the availability of the Tribe thesis. According to Dr. Tribe, who received his Ph.D. degree from the University of Melbourne in July 1977, each of the following were sent a copy of his thesis around May 1977:(1) the Baillieu Library at the University of Melbourne; (2) the Heather Jenkins Research Library of the University of Melbourne Department of Microbiology; (3) Professor H.A. Pittard at the University of Melbourne; and (4) Professor Arnold Demane at the Massachusetts Institute of Technology. (D.I. 314 at 1200) Dr. Tribe testified, based on his personal knowledge, that in 1977 both of the libraries had a card catalogue system and were open to the public. (D.I. 314 at 1201-04)

34. At trial, Dr. Tribe had with him a bound copy of his thesis bearing a date stamped by the Heather Jenkins Research Library of October 28, 1977, a copy of which was submitted into evidence. (DX 383) This date-stamped copy was not provided to Ajinomoto during discovery. (D.I. 314 at 1193) According to Dr. Tribe, this date-stamp reflects when the thesis was received, catalogued, and shelved by the Heather Jenkins Research Library. (D.I. 314 at 1200-02) Dr. Tribe testified that his thesis presently is listed in the card catalogue system at the Heather Jenkins Research Library and that he had no reason to believe that his thesis was not accessible to members of the public prior to June 1978. (D.I. 314 at 1200-03)

35. With respect to the copy of the Tribe thesis located in the Baillieu Library, Dr. Tribe testified that he believed his thesis to be listed in the card catalogue system although he had "not directly examined the card index system." (D.I. 314 at 1204) Nevertheless, he stated that he "physically [has] looked at [his] thesis in the [Baillieu] Library." (D.I. 314 at 1205) According to Dr. Tribe, it was his understanding that it takes approximately six months for the Baillieu Library to place items it receives, such as his dissertation, on the shelves. (D.I. 314 at 1205) Dr. Tribe testified that it was his belief that his thesis was placed in the Baillieu Library card catalogue system and was accessible to the public prior to June 1978. (D.I. 314 at 1205-07)

36. However, on cross-examination Dr. Tribe admitted that he was not at the University of Melbourne for most of 1977 and 1978 and that, therefore, there were "many details of the cataloguing with which [he] would not be familiar." (D.I. 314 at 1230)

37. Dr. Tribe also testified that he presented publicly

his research findings in the United States on three different occasions prior to June 30, 1978. The first was at the Third Genetics of Industrial Microorganisms Conference, which was held in Madison, Wisconsin in early June 1978. (D.I. 314 at 1214-15) This conference was attended by approximately thirty to forty people. (D.I. 314 at 1214-15) According to Dr. Tribe, the presentation covered "getting bacteria [[[[ ] to make large amounts of tryptophan." (D.I. 314 at 1215) Dr. Tribe noted that a speaker from Genetika was present at this conference. (D.I. 314 at 1216) Dr. Tribe's second presentation of his findings was at CPC International in Argo, Illinois, also in June 1978. (D.I. 314 at 1216-17) This presentation was attended by approximately 20 industrial workers and covered "getting bacteria by genetic manipulation to make large amounts of tryptophan." (D.I. 314 at 1216-17) The third presentation was in late June 1978 (but before June 30) at the University of Rochester to a group of graduate students and faculty. (D.I. 314 at 1217-18) According to Dr. Tribe, the presentation covered that part of his thesis dealing with "getting bacteria to manufacture tryptophan." (D.I. 314 at 1217-18)

***11** 38. According to Dr. Tribe, other presentations of research covered by his doctoral thesis include: (1) the First Australian Biotechnology Conference in Sydney, Australia in 1975 (an oral presentation of a "substantial portion of [his] findings in how to get bacteria to make large amounts of tryptophan"); (2) a paper presented at the Australian Biochemical Society meeting in May 1975 and published in abstract form in the Proceedings of the Australian Biochemical Society (reporting the "first half of [the] major findings in [his] thesis"); and (3) a paper published in the Journal of Bacteriology in 1976 (covering the "major section of the results ... in [his] thesis and report[ing] them in considerable detail"). (D.I. 314 at 1211-1212)

39. **The Teachings of the Tribe Thesis.** The Tribe thesis discusses the combining of a chromosome DNA fragment (JP2278) containing genes controlling the synthesis of an amino acid (tryptophan), having a mutation (*trpE382*) that destroys the negative regulation of tryptophan, with a plasmid (F'123) as set forth in claim 1 of the '765 patent. (D.I. 313 at 1016) In contrast to the '765 patent, which called for the use of a plasmid capable of ensuring amplification, the F' plasmid employed by Tribe is a stringent plasmid, which is present in the cell in one or at most two copies.[FN17] (D.I. 314 at 1104; D.I. 316 at 1522, 1528; D.I. 317 at 1654-60) This type of plasmid, although it can be isolated as an independent entity from the cell, cannot replicate independently from the cell; it only replicates in synchrony with the chromosome.[FN18] (D.I. 316 at 1522) Moreover, whereas the '765 patent teaches *in vitro* techniques of molecular recombination for producing a hybrid plasmid, the hybrid plasmid in the Tribe thesis is formed using *in vivo* recombination/transduction. (D.I. 314 at 1105-06; D.I. 316 at 1528-29; D.I. 317 at 1661)

FN17. In asserting that the F' plasmid used by Dr. Tribe was capable of amplification, ADM relies on a statement appearing in a textbook on bacterial genetics that "in a rapidly growing cell, the number of F prime plasmids must, of course, be larger than two to allow for the shorter time between cell divisions." (D.I. 316 at 1558-1559; D .I. 317 at 1627) When questioned regarding this assertion, Dr. Falkinham explained that replication of F' plasmids is initiated with that of the chromosome but because of their smaller size (5% of the chromosome) their replication takes a shorter period of time. (D .I. 316 at 1559) Thus, according to Dr. Falkinham, one would expect to find between one and two copies of F' plasmids per chromosome equivalent in a rapidly growing cell. (D.I. 316 at 1559)

FN18. Dr. Tribe did recognize that manipulating the number of copies of the plasmid might further improve tryptophan yield. (D.I. 383 at 177) In his summary, Dr. Tribe stated that "increases in tryptophan yield were obtained by amplification of ... tryptophan enzyme levels through introduction of extra, plasmid borne copies of *trp* genes." (D.I. 383 at iii) In addition, he recognized that work was underway "towards obtaining mutants of the multi-copy plasmid ColEl'-*trp* ... in which the anthranilate synthase encoded by the [plasmid's] *trp* genes is feedback resistant," but that there were problems with this approach. (D.I. 383 at 144)

40. Tribe also teaches the insertion of a hybrid plasmid into a recipient bacterial strain that has a mutation (*trpE5*) completely blocking the synthesis of the selected amino acid. In contrast to the '765 patent, which employed transformation in this step, the hybrid F' plasmid used by Tribe entered the

recipient bacterial cell via conjugation (the F'521 plasmid being too large for transformation). (D.I. 307 at 113; D.I. 308 at 321-22; D.I. 313 at 1013-16, 1019; D.I. 316 at 1561; D.I. 317 at 1662) Conjugation is a natural "mating" process involving cell-to-cell contact between the donor and the recipient E. coli cells and the transfer of genetic material, in this case the plasmid. (D.I. 316 at 1016) In contrast to conjugation, transformation, as defined in the '765 patent, involves the "transfer of genetic bacterial material to a bacterial cell by means of isolated DNA." (JX 1 at col. 1, lines 19-20)

41. Tribe employed an auxotrophic host strain for the same purpose as did the '765 inventors: to make it easier to select bacterial strains containing the hybrid plasmid carrying the genes for the synthesis of the selected amino acid. (D.I. 314 at 1102; D.I. 317 at 1653-54; JX 1 at col. 5, lines 43-47) Tribe does not teach the use of an auxotrophic host for the over expression of tryptophan; rather Tribe affirmatively stated that one should use a non-auxotrophic host, because it would increase gene number. (D.I. 316 at 1523; D.I. 317 at 1654; D.I. 314 at 1102; D.I. 316 at 1523) Nowhere in the Tribe thesis is it suggested that an auxotrophic host be used in the over production of the selected amino acid. (D.I. 314 at 1102)

***12** 42. Tribe does not teach the use of a mutation partly blocking the related step of metabolism of the selected amino acid. Rather, the tryptophanase auxotrophy disclosed in the Tribe thesis is a complete block. (D.I. 316 at 1522; D.I. 317 at 1658) In fact, according to Dr. Frederick B. Rudolph (ADM's expert witness), Tribe stressed that a complete block was desired because metabolism of the amino acid was to be avoided. (D.I. 314 at 1109; D.I. 317 at 1658)

43. Tribe does teach the use of a recipient strain carrying a *trpS378* mutation. The *trpS378* mutation is a temperature sensitive mutation,[FN19] the phenotypic expression of which appears at temperatures greater than 37 degrees Celsius. (D.I. 316 at 1528) According to Dr. Rudolph, the benefit of the *trpS378* mutation is that at higher temperatures (42 degrees Celsius or higher) the enzymatic activity of the product of the *trpS378* gene decreases, thereby increasing the level of tryptophanol-tRNA which lowers the level of repression of the tryptophan operon.[FN20] (D.I. 317 at 1621-23, 1657) Derepression of the tryptophan operon has the effect of increasing tryptophan pathway enzyme levels, ultimately resulting in an increase in tryptophan production. (D.I. 317 at 1621-23, 1657) Although Dr. Rudolph initially stated that the *trpS378* mutation was a mutation partially blocking the related step of metabolism of tryptophan (D.I. 313 at 1018-19), on rebuttal cross-examination he indicated that such was not really the case, but that the mutation was "very analogous to the isoleucine part in that the isoleucine does exactly the same thing." (D.I. 317 at 1657-58) He went on to state that Dr. Tribe's focus on the *trpS378* mutation was not for its role in blocking a related step in metabolism, but for its role in derepressing the tryptophan operon. (D.I. 317 at 1658)

> FN19. A temperature sensitive mutation is one whose enzymatic activity is affected by the temperature. (D.I. 317 at 1621-23)
>
> FN20. According to Dr. Falkinham, E. coli were normally grown at 37 degrees Celsius. (D.I. 316 at 1527) Dr. Falkinham also testified that one would not grow E. coli at 42 degrees Celsius for commercial production because at higher temperatures bacteria stop growing and proteins denature. (D.I. 316 at 1526-27)

44. Dr. Rudolph ultimately conceded that not a single strain constructed by Dr. Tribe had all the characteristics set forth in claim 1 of the '765 patent. (D.I. 317 at 1653) And as indicated in a letter dated February 6, 1990 from ADM's George Stauffer to John Reed, then ADM's Vice President of International, following their meeting with Genetika, both of the characteristics of the recipient strain set forth in claim 1 (i.e., a mutation blocking the synthesis of the selected amino acid and a mutation partly blocking the related step of metabolism of the amino acid) are "important advantage[s]" of the Genetika strains. (JX 12)

45. *The Kozlov Article: Availability.* It is undisputed that the Kozlov article, which was authored by several of the '765 inventors, is prior art. (DX 321) This article was referenced in the specification of the '765 patent. (JX 1 at col. 1, lines 56-58). A copy of this publication was not provided to the PTO by the inventors during the prosecution of the patent.

46. **The Teachings of the Kozlov Article.** The Kozlov article teaches a method for the isolation of specific chromosomal markers whereby, using *in vitro* techniques, a chromosomal DNA fragment

containing some of the genes necessary for amino acid production [FN21] is ligated with amplifiable plasmid DNA forming a hybrid plasmid that is used to transform an auxotrophic host strain.

FN21. Because Kozlov used the endonuclease EcoRI in the digestion of the chromosomal DNA, the chromosomal threonine marker which resulted contained only functional *thrA* and *thrB* genes rather than the complete threonine operon. (D.I. 316 at 1520-21) This incomplete threonine operon was not feedback resistant. (D.I. 316 at 1521) However, had Kozlov used the restriction enzyme HindIII, he would have isolated a chromosome DNA fragment containing *thrA, thrB,* and *thrC* genes, i.e., the complete threonine operon. (D.I. 316 at 1563) The '765 patent disclosed the use of HindIII to digest chromosomal DNA although the '765 inventors were not the first to do so. (D.I. 316 at 1564)

***13** 47. With respect to claim 1, the Kozlov article does not teach: (1) the creation of a bacterial strain capable of over production of a selected amino acid; (2) the use of a chromosomal DNA fragment containing "the genes controlling the synthesis of a selected amino acid"; (3) the use of a chromosomal DNA fragment having a mutation making it feedback resistant; and (4) a recipient strain having a mutation partly blocking the related step of metabolism of the selected amino acid. (D.I. 316 at 1519-22; D.I. 317 at 1649-50)

48. **Genetika I & II:** [FN22] **Availability.** The court has previously concluded in its decision of October 21, 1996 that the Genetika articles were prior art, finding that there existed sufficient indicia of their availability. [FN23] (D.I. 272 at 45) Copies of these articles were not submitted to the PTO during the prosecution of the '765 patent. However, Genetika II was listed in the reference section and cited to in the specification of the Russian priority patent, a certified English translation of which was provided to the PTO as part of the U.S. patent application. (PX 2)

FN22. Dr. Rudolph, in his expert report, treated the two Genetika articles as equivalent and thus cumulative of each other. (D.I. 201, Ex. Q at ¶ 15) Therefore, the citation to one or the other is sufficient. *See Halliburton co. v. Schlumberger Technology Corp.*, 925 F.2d 1435, 1440 (Fed.Cir.1991).

FN23. Ajinomoto contests the court's holding of the prior art status of the Genetika articles, arguing that the court mistakenly relied upon incomplete information in reaching its conclusion that the references, which are cited in the Russian priority patent, were publicly available. (D.I. 323 at 49) The "complete" information referred to by Ajinomoto includes two copies of the articles bearing U.S. library date stamps of September 1978 and Dr. Debabov's deposition testimony that the inventors knew of the citations prior to publication and included them in the patent application even though the articles were not publicly available. (D.I. 323 at 49-50)

49. **The Teachings of the Genetika Articles.** The Genetika articles describe the relevance of the allelic state of the *relA* gene to the over synthesis of threonine. These publications also describe the donor and recipient E. coli strains used in the examples of the '765 patent. Both Genetika I and II describe the strain MG442, the donor strain in the '765 patent, as containing the genes controlling threonine production, having a mutation (*thrA442*) destroying the negative feedback regulation of threonine synthesis, and having a mutation (*ilvA*) partly blocking a related step of threonine metabolism. (D.I. 313 at 1023-25; D.I. 317 at 1632-1636; DX 305 at 671; DX 326 at 664) In addition, Genetika I describes the strain VL334, the recipient strain in the '765 patent, as having a mutation (*thrC1010*) blocking the synthesis of threonine and a mutation (*ilvA442*) partly blocking a related step in the metabolism of threonine. (D.I. 313 at 1023-25; D.I. 317 at 1632-1636; DX 326 at 661, 664) Genetika II teaches that the two mutations found in MG442-a mutation destroying feedback resistance (*thrA442*) and a mutation partly blocking the related step of metabolism (*ilvA*)-positively contribute to threonine over production. (DX 305 at 675)

50. Genetika I and II do not teach or suggest the claimed invention. As admitted by Dr. Rudolph on cross-examination, neither Genetika I nor Genetika II mention or suggest the use of plasmids or the construction of plasmids, much less the formation of hybrid plasmids. (D.I. 317 at 1640-41) In addition, neither publication discusses the isolation or increase in copy number of a feedback resistant operon or the use of an auxotrophic host for the production of

threonine. (D.I. 316 at 1518)

51. **The Clarke/Carbon Article: Availability.** The Clarke/Carbon Article was published in November 1975 and was referenced in the specification of the '765 patent, although a copy of the article was not provided to the PTO during the prosecution of the '765 patent. (JX 1 at col. 1, lines 52-53)

***14** 52. **The Teachings of the Clarke/Carbon Article.** The Clarke/Carbon article discusses a method using *in vitro* techniques for the isolation of specific segments of the E. coli genome similar to that set forth in the Kozlov article. The article teaches the digestion of plasmids and E. coli DNA with an endonuclease, followed by treatment with an exonuclease and then attachment of "connectors." (DX 290 at 4362) The mixture of annealed, but not ligated, hybrid DNA was used to transform E. coli auxotrophs, followed by selection for a specific chromosomal marker. (DX 290 at 4362) The isolated bacterial strains contained hybrid plasmids carrying either the entire tryptophan or the arabinose and leucine operons. (DX 290 at 4364) According to Clarke/Carbon, the bacterial strains containing the hybrid plasmids carrying the tryptophan operon produced elevated levels of trp-mRNA. (DX 209 at 4364) However, increased levels of tryptophan production were not reported.

53. With respect to claim 2, the last paragraph of the discussion section of the Clarke/Carbon article mentions, as one of the advantages in having gene systems isolated and cloned on plasmids carried by bacteria, that
hybrid plasmids containing specific E. coli genes may be easily manipulated or made smaller by shearing or endonuclease digestion. New vectors can then be isolated which bear known E. coli gene systems that may be useful in the isolation and cloning of genes from other organisms. Thus, the insertion of foreign DNA into an E. coli operon, bringing the expression of that DNA under control of bacterial regulatory sequences, should be readily achieved.

(DX 290 at 4365; D.I. 313 at 1023) According to Dr. Rudolph, the Clarke/Carbon article, by stating that hybrid plasmids can be made smaller by endonuclease digestion, rendered the ballast removal step of claim 2 of the '765 patent obvious. (D.I. 313 at 1022-23)

E. The Scope of the '765 Patent

54. Claims 1 and 2 of the '765 patent are generic claims directed to a method of constructing a microorganism capable of producing any amino acid.

55. At the time of the invention, approximately 50,000 different bacterial species were thought to exist, of which approximately 4000 had been identified. (D.I. 314 at 1178-80) There are twenty amino acids. (D.I. 307 at 105; D.I. 313 at 959) Thus, in theory, the process of claims 1 and 2 of the '765 patent covers at least 1 million possible different combinations of bacterial species and amino acids.

56. The specification of the '765 patent sets forth specific methods for preparing a single strain of E. coli bacteria capable of overproducing the amino acid threonine. (JX 1)

57. Prior to becoming the assignee of the '765 patent, Ajinomoto argued, during the prosecution of seven patent applications, that the specification of the '765 patent did not enable the full scope of the claims. (PX 218; PX 219; PX 221; PX 222; PX 223; PX 224; PX 225) However, in each instance, the PTO Examiner rejected Ajinomoto's argument, finding that the patent was enabled since the types of mutations suggested by the patent were conventional and one skilled in the art could easily produce such mutants because genetic engineering techniques were conventional and well-known. (PX 218 at 98-101, 128, 219-221; PX 219 at 119-20; PX 221 at 65-6; PX 222 at 139; PX 223 at 89-90; PX 224 at 106-07; PX 225 at 106-07) In particular, various PTO Examiners stated at various times:
***15** One skilled in the art could practice the invention using as the DNA donor any microorganism having a mutation in the negative regulation of the synthesis of the amino acid and as the recipient a microorganism which has a mutation partly blocking a related step of the metabolism of the amino acid. No particular organisms are required as evidenced by claims 1 and 2 of [the '765 [patent] which are not restricted to any microorganisms. **The types of mutations suggested by [the '765 patent] are conventional and have been used repeatedly to cause microorganisms to produce more amino acid product. The literature is replete with microorganisms which could be used.** [The '765 patent's] contribution was using genetic engineering to produce another microorganism.

(PX 218 at 220) (emphasis added).**The methods taught by [the '765 patent] are predictable and can be practiced with starting materials cited in**

the patent, or their well-know[n] equivalents, all available to one of ordinary skill in the art.
... When a case involves *starting materials which are already known and available to persons in the art at the time of filing* an application for patent, the description need not contain an enabling disclosure of them ...
Ex parte Argoudelis[,] 157 USPQ 437[,] 441

(PX 223 at 88) (alteration in original) (emphasis added).[The '765 patent] provides an adequate disclosure for one skilled in the art to practice the invention whether or not the microorganism is available.... In order to practice the invention of [the '765 patent] to make any amino acid, one skilled in the art could use any mutant which has the characteristics disclosed by the patent and successfully produce amino acids.

(PX 222 at 139) (emphasis added).**Such mutant strains for a particular amino acid are well known in the art and their use would be obvious.** Moreover, the broad claims are not restricted to any particular strains.

[The '765 patent] **provides an adequate teaching to one skilled in the art to produce any amino acid from available mutants.**

(PX 224 at 106-07) (emphasis added).Claims 1-18 are rejected under 35 U.S.C. 103 as unpatentable over [the '765 patent] ... [which shows] producing amino acids by combining the DNA of a donor microorganism, such as E. coli, which has a mutation in the genes destroying the negative feedback, such as being resistant to an analogue of the amino acid, with a vector and transforming an E. coli mutant, which requires an amino acid, with the hybrid DNA to increase the amino acid production. The production of any amino acid, such as L-glutamic acid, and the aprop[ri]ate mutant would be obvious since **such mutation techniques are conventional and well known.**

(PX 219 at 140) (emphasis added).

58. **Elements of Claims 1 and 2.** In order to practice claims 1 and 2 of the '765 patent, a single chromosome fragment containing the genes controlling the synthesis of the selected amino acid must be isolated and obtained. (JX 1) According to Dr. Rudolph, in the late 1970's the biochemical pathways for amino acid synthesis in all bacterial species were not known; in particular, the method of regulation of the pathways was not known. (D.I. 313 at 939, 948, 1008-09; D.I. 314 at 1179-80) Although the steps in the biosynthetic pathway of an amino acid are generally the same across species, the regulation method varies from species to species. (D.I. 313 at 948) For example, the genes controlling the synthesis of threonine in E. coli differ from those in *Corynebacteria,* as does the method of regulation. (D.I. 314 at 944-48) In fact, some bacterial species cannot make certain amino acids. (D.I. 301 at 100)

***16** 59. Both Dr. Falkinham and Dr. Rudolph agreed that claim 1 calls for a single chromosome fragment containing the genes controlling the synthesis of a selected amino acid. (D.I. 308 at 311; D.I. 313 at 950-02, 963, 997) To isolate such a fragment, said genes must be contiguous. (D.I. 308 at 311; D.I. 313 at 963) However, all the genes controlling the synthesis of a selected amino acid are not always contiguous. (D.I. 313 at 1016; D.I. 313 at 947, 954, 997-98, 1009, 1041; DX 495) For example, although in E. coli the three genes of the threonine operon are contiguous as are the five genes of the tryptophan operon and the nine genes of the histidine operon, the genes controlling the synthesis of arginine and methionine are not contiguous. (D.I. 308 at 301; D.I. 313 at 997) And in *Brevibacteria* and *Corynebacteria,* the genes controlling the synthesis of threonine are located on separate, noncontiguous segments of the chromosome. (D.I. 313 at 944-48; DX 495; DX 1108 at 80) In fact, in E. coli, the *asd* gene, the product of which catalyzes the second step in the threonine pathway, is not contiguous with the genes of the threonine operon. (D.I. 313 at 947, 953-54, 1041, 1060-61; D.I. 314 at 1169) Therefore, with respect to E. coli, a single chromosome fragment cannot contain the *asd* gene and the threonine operon. (D.I. 308 at 323-24; D.I. 313 at 947, 1060-61)

60. In order to isolate the desired chromosome fragment, the appropriate restriction endonuclease must be employed. (D.I. 307 at 114-116; D.I. 313 at 950-53) Each endonuclease recognizes a unique sequence of basepairs in DNA, cutting only at those sites; therefore, cutting a particular DNA molecule with a particular restriction enzyme, such as BamHI or EcoRI, always yields a particular group of fragments. (D.I. 307 at 114-16) Once obtained, these fragments can be inserted into a plasmid that has been cleaved using the same restriction endonuclease, thereby generating insertion sites. (D.I. 313 at 950-53)

61. To isolate the hybrid plasmid carrying the

chromosome fragment of interest, the plasmids are inserted into a recipient bacterial strain that is auxotrophic for the selected amino acid; through a complementation process (growth on a medium devoid of the desired amino acid), it is determined whether the hybrid plasmid carries the genes of interest. (D.I. 313 at 950-53) If the desired chromosome fragment is not isolated, the process must be repeated using a different restriction endonuclease. (D.I. 313 at 950-53) According to Dr. Rudolph, these techniques are routinely performed in the laboratory and it takes approximately one day to conduct one such sequence, from digestion with the restriction enzyme to selection of the desired strain. (D.I. 313 at 1058-59)

62. On cross examination, Dr. Rudolph testified that as of 1978 one of ordinary skill in the art would be able to use the basic *in vitro* techniques necessary for recombinant cloning, including how to use ligase and a ligation reaction and how to conduct restriction digest using restriction endonucleases. (D.I. 313 at 1047)

***17** 63. Claim 1 of the '765 patent requires the use of a plasmid suitable for constructing a hybrid plasmid for transforming another bacterial strain. (JX 1) Although at the time of the invention, E. coli was well characterized and the plasmid pBR322 was readily available, plasmids suitable for making hybrid plasmids capable of transforming other bacterial species were not as well developed. (D.I. 313 at 998-99, 1007, 1009) According to an article authored by Dr. Debabov entitled *Advances in the Genetic Engineering of Microorganisms,* "[t]he extension of genetic engineering techniques to ... microorganisms [other than E. coli] requires additional investigation." (DX 165; DX 1100 at 132-33) Thus, at the time of the invention, the technology with respect to E. coli was more developed than it was for other industrial microorganisms. (DX 1100 at 132-33) For example, Dr. Rudolph testified that based on his experience with the bacteria *Clostridium,* plasmids suitable for use in transformation are not known for all bacterial species and therefore must be developed. (D.I. 313 at 998-9, 1007, 1009)

64. At the time of the invention, transformation techniques available for E. coli, although relatively well-known, were not universally applicable to other bacteria. (D.I. 313 at 958, 998-99, 1009, 1047) Dr. Rudolph testified that at that time he "had trouble in his own work with transformation." (D.I. 313 at 1048) According to an article authored by Konosuke Sano, senior chief scientist at Ajinomoto, entitled *Host-Vector Systems for Animo Acid-Producing Coryneform Bacteria,* the development of a host-vector system was necessary before recombinant DNA technology could be applied to *Coryneform* bacteria because the E. coli systems were not available. (DX 102 at 486) This concern was reiterated by Shukuo Kinoshita in a chapter he authored in *Biology of Industrial Microorganisms,* in which he stated that there exist various problems hindering the application of recombinant DNA technology for improving *Coryneform* glutamic acid producing bacteria. (DX 373 at 124-26) Similarly, Kiyoshi Miwa, head of the Pharmaceutical Biomedical Research Laboratory of the Applied Research Division of the Central Research Laboratory of Ajinomoto, admitted there were points which had to be "overcome" with respect to the expression of heterologous genes in *Coryneform* bacteria using plasmids capable of transforming the bacteria. (DX 1109 at 109-11, 117)

65. Claim 2 of the '765 patent requires the use of a recipient bacterial strain having a mutation blocking the synthesis of the selected amino acid and a mutation partly blocking the related step of metabolism of said amino acid. (JX 1) The patent does not disclose the extent of the partial block necessary to practice the claimed invention or how to isolate a bacterial strain containing the two required mutations. (D.I. 313 at 1000-03, 1010-11, 1049-53; D.I. 314 at 1091-94, 1165, 1178) Even Genetika reported difficulty creating an *ilvA* mutation in two strains of bacteria, VL1991 and a derivative VL1997. (DX 79 at 9096)

***18** 66. Dr. Rudolph testified on cross-examination that one of ordinary skill in the art at the time of the invention would know how to use nitrosoguanidine as a mutagen to make specific mutants. (D.I. 313 at 1048) In addition, he testified that at the time of the invention, feedback resistant mutants were known in the literature. (D.I. 313 at 1049-50) He further opined that one skilled in the art **should** be able to isolate amino acid auxotrophic mutants, but that the ability to do so might vary from amino acid to amino acid and strain to strain. (D.I. 313 at 1049-50) Dr. Rudolph also opined that, in the context of the Tribe thesis and E. coli, one skilled in art at the time of the invention could have carried out these mutations for all twenty of the amino acids. (D.I.1052-53)

F. The Availability of the Strains

67. There are four strains mentioned in the claims of

the '765 patent: the donor strain MG442, the recipient strain VL334, and two product strains, VL334 (pYN6) and VL334 (pYN7). These strains are further identified by the registration numbers given them by the Central Museum, as follows:

Strain	Registration No.
MG442	CMIM B-1628
VL334	CMIM B-1641
VL334	(pYN6) CMIM B-1649
VL334	(pYN7) CMIM B-1684

68. During the prosecution of four patent applications submitted by Ajinomoto prior to its acquisition of the '765 patent, the PTO Examiners specifically found that the strains were available to the public. (PX 223 at 89) The PTO Examiners also found the '765 patent to be enabled without the required deposits:

> Moreover, and in any case, the teaching in [the '765 patent] is considered sufficient to enable the ordinary skilled artisan to practice the ['765 patent] **even where the specific mentioned starting microorganism and host microorganisms are not available.** Analogous microorganisms are well known and access thereto is readily avail[a]ble.

(PX 218 at 100-01) (emphasis added).[The '765 patent] provides an adequate disclosure for one skilled in the art to practice the invention **whether or not the microorganism is available** and applicants have not shown that it is not. In order to practice the invention of [the '765 patent] to make any amino acid, one skilled in the art could use any mutant which has the characteristics disclosed by the patent and successfully produce amino acids.

(PX 222 at 139) (emphasis added); (PX 219 at 119-20).

69. Dr. Rudolph testified that dependent claims 3 and 4 were enabled without deposits. (D.I. 314 at 1115-16)

70. **The Degussa Inquiry.** On March 3, 1994 Degussa, a German company that competes with Ajinomoto and ADM in the threonine industry, wrote to Genetika inquiring about the formal requirements that must be fulfilled and the fees required to obtain various bacterial strains, including VL334 (pYN7). (D.I. 315 at 1376-79; DX 88 at 25386) This inquiry did not conform with the Budapest Treaty on the International Recognition of the Deposit of Microorganism for the Purpose of Patent Procedure.[FN24]

> FN24. The Budapest Treaty on the International Recognition of the Deposit of Microorganism for the Purpose of Patent Procedure governs the proper method of making a biological deposit, the accepted depositories, and the proper procedures to be followed for requesting a deposit. With respect to the United States, the Budapest Treaty entered into force on August 19, 1980. (D.I.98, Ex. 1) The former Soviet Union did not join the Budapest Treaty until April 22, 1981. (D.I.98, Ex. 1) The strain VL334 (pYN7) was deposited in 1978. (DX 156 at 58, 125) According to Dr. Paraskevov, if Genetika received a request for deposited threonine-producing strains that conformed with the Budapest Treaty, it was obliged to supply the strain without first contacting Ajinomoto. (DX 1118 at 48-53) However, if the request was non-conforming, then Genetika would consult with Ajinomoto because Ajinomoto had the exclusive rights to the strains. (DX 1118 at 48-53)

***19** 71. In accordance with Genetika's agreement to provide Ajinomoto with information on contacts between Degussa and Genetika, for which Genetika was paid $20,000, Genetika's Dr. Paraskevov informed *Yoshikazu* Takayanagi, then section manager of Ajinomoto's Patent and Licensing Department, of the request. (D.I. 315 at 1359, 1376-79; DX 88) In a letter dated March 18, 1994, Mr. Takayanagi told Dr. Paraskevov that he believed Dr. Paraskevov to be "under no obligation to provide [ ] such strains to Degussa ... because these strains of Degussa's request are not the subject matters of German patents." (D.I. 315 at 1383; DX 89 at 1) In addition, as was common practice between Ajinomoto and Genetika, Mr. Takayanagi provided Dr. Paraskevov with suggested language to use in response letters to Degussa:

> Meanwhile please respond to Degussa as follows:
> "We duly received your letter of March 2, and March 16, 1994, now we are consulting this matter with Russian Ministry of Technology and Science and Russian Patent Office, so [ ] please give us a few weeks for our definitive reply to you[.]"
> [A]nd a few weeks later you will send the second letter to Degussa indicating that: "Upon instruction of Russian Ministry of Technology and Science and Russian Patent Office, we regret to inform you that we are determined not to provide[ ] you with the strains of your request.

(D.I. 315 at 1383-85; DX 89 at 1) In a subsequent letter to Dr. Paraskevov dated June 8, 1994, Mr Takayanagi told him to "please send a refusing letter to Degussa.... We think the purpose of Degussa is to obtain strains from you under no obligation and to modify them to patent free strains for use by Biotika or Fermas." (DX 91)

When Degussa sent Genetika a request conforming to the Budapest Treaty on January 8, 1996, it was told it would receive the samples. (DX 167; DX 1118 at 43-44)

72. **The Pardo Inquiry.** In January 1994, Dr. Daniel Pardo of Eurolysine wrote to Genetika inquiring as to the procedure for ordering the bacterial strain B3996. (DX 168 at 3) No other strain was mentioned in the body of the letter. However, an attachment to the letter entitled "List of VNII Genetika E. coli strains" lists seven strains; item number 3 on this list is the strain VL334 (pYN7). (DX 168 at 4) Listed as item number 7 is the strain B3996. (DX 168 at 4) Of the items listed, only this item has the notation following it: "Please confirm the availability of this strain since it was deposited for patent purpose ..." (DX 168 at 4)

73. On January 26, 1994, Mr. Paraskevov sent Mr. Takayanagi a copy of Dr. Pardo's request, inquiring as to how Genetika should proceed. (DX 168 at 1) Mr. Takayanagi replied that Dr. Paraskevov had "no legal obligation[ ] to comply with the request of Dr. Pardo," advising Dr. Paraskevov to ignore the request for the moment. (DX 137 at 1; D.I. 315 at 1388) On February 4, 1994, Mr. Takayanagi reiterated to Dr. Paraskevov that he should "feel no responsibility to respond to or comply with the letter of Dr. Pardo dated January 21, 1994, unless or until you receive a[ ] official letter with a certificate of French Patent Office from him." (DX 95 at 1) Mr. Takayanagi went on to state that "among the strains of Dr. Pardo's request, the strain under international deposit is only VKPM B-3996, all other strains are domestic deposit under [U.S.S.R.] or Russian Laws, so that you will refuse to furnish him these strains citing appropriate Russian laws." (DX 95 at 1)

***20** 74. Dr. Pardo's inquiry, also, did not conform with the Budapest Treaty.[FN25]

FN25. The court granted Ajinomoto's motion *in limine* "to exclude the testimony of and documents relating to Dr. Andrei Sibirny" and his request for strains. (D.I. 278 at ¶ 5)

G. The Role of relA in the Over Production of Threonine

75. The court has already recognized that "the best mode of practicing the '765 invention requires that the bacterial host be characterized by the presence of a *relA* $^{+}$ gene." (D.I. 274 at 42) The specification does not explicitly characterize the bacterial host by the presence of a *relA* $^{+}$ gene or disclose the importance of this gene. (D.I. 274 at 42)

76. **The Relevance of the relA gene.** At the time of the invention, it was known to one of ordinary skill in the art that under conditions of amino acid starvation the operons of **certain** amino acids were positively regulated by the product of the wild type allele of the *relA* gene. (D.I. 314 at 1088-89; D.I. 316 at 1512; DX 326 at 660, 665; DX 305 at 668, 675)

77. The significance of the *relA* gene with respect to the synthesis of threonine was reported by some of the inventors of the '765 patent in Genetika I and Genetika II, which were published at the time the '765 patent application was filed. (DX 326; DX 305) Both publications discuss the relevance of the allelic state of the *relA* gene to the phenotypic expression of certain mutations in the threonine operon (*thrA442*) and the isoleucine-valine operon (*ilvA*) and the over synthesis of threonine. Each concludes that the operons controlling threonine and isoleucine synthesis are positively regulated by the product of the wild type *relA* gene and that under conditions of isoleucine deficiency, the wild allele of the *relA* gene has a positive influence on the over synthesis of threonine. (DX 305 at 675-76; DX 326 at 665-66) Thus, these publications disclose that the threonine operon is one of those amino acid operons the transcription of which is stimulated by the product of wild type *relA* gene. It is undisputed that not all E. coli strains have the *relA* $^{+}$ gene. (D.I. 313 at 996; D.I. 316 at 1533)

According to Dr. Rudolph, one of ordinary skill in the art being familiar with the literature, particularly the Debabov article and Genetika I and II, would have been able to determine the best mode of practicing the '765 invention. (D.I. 314 at 1088) Dr. Falkinham goes one step further concluding that one of ordinary skill in the art would have known that *relA* $^{+}$ is required to practice the claimed invention. (D.I. 316 at 1512)

78. **The Presence of relA $^{+}$ in Leaky Auxotrophs.** According to Genetika I and II, "introduction of the *relA* mutation into the genome of semiauxotrophic strains with respect to threonine and isoleucine leads to the appearance of a strict dependence of their growth on the presence of those amino acids in the medium." (DX 326 at 665; DX 305 at 675) Through a series of experiments, the researchers concluded that the effect of the *relA* $^{-}$ gene

on a leaky auxotroph is to make it a complete auxotroph. (D.I. 313 at 993; D.I. 314 at 1090; D.I. 316 at 1533-38; D.I. 317 at 1638, 1643-44; DX 305; DX 326) Therefore, as reiterated by Dr. Falkinham, the literature supports a finding that the *relA* $^{+}$ gene is inherently present whenever a leaky mutation is obtained. (D.I. 316 at 1512, 1515)

***21** 79. The inventors of the '765 patent disclosed the preparation of strains VL334 (pYN6) and VL334 (pYN7), the only strains at the time of the '765 patent application reduced to practice. It is undisputed that the parent strain of VL334 is MG442, a *relA* $^{+}$ strain. (D.I. 313 at 992-93; D.I. 314 at 1091) According to Dr. Falkinham, in the absence of any indication that there was a change in the allelic state of the *relA* gene, one skilled in the art would conclude that VL334 was also *relA* $^{+}$ (D.I. 316 at 1512, 1540-41)

80. **Bacterial Strain Nomenclature.** According to Dr. Falkinham, the general practice in describing the genetic characteristics of bacterial strains is to list only mutations of genes; thus, anyone skilled in the art reading the specification of the '765 patent would know, since none of the recipient strains contain the *relA* gene in their description, that the strains are *relA* $^{+}$. (D.I. 316 at 1540-41) This "practice" is not followed by the inventors to the extent that they did not disclose in the '765 patent the *supE* gene (the amber mutation), a common mutation in the early strains of E. coli K-12, even though it is mutated in VL334. (D.I. 316 at 1575; DX 305 at 669; DX 326 at 661) Therefore, it cannot be concluded that the allelic state of the *relA* gene was disclosed through the nomenclature employed in the '765 patent.

H. Genetika's Threonine-Producing Bacterial Strains

81. According to the '765 patent, the plasmid pYN7 is constructed from either pYN6 or pYN10 using the '765 process. Either plasmid is treated with specific endonuclease followed by treatment with a polynucleotide ligase. (JX 1 at col. 10, lines 17-22) The resulting preparation is used for transformation, and clones with a specific phenotype are selected. (JX 1 at col. 10, lines 22-25) The plasmid with molecular weight 5.7 megadaltons (Md), [FN26] pYN7, was isolated from an arbitrarily selected clone. (JX 1 at col. 10, lines 25-27) This hybrid plasmid is composed of two fragments, the greater portion corresponding to the plasmid pBR322 and the other a fragment of DNA chromosome of the strain MG442 containing all of the genes of the threonine operon. (JX 1 at col. 10, lines 27-36) The plasmid pYN7 is used for transformation of the strain E. coli VL334, which has mutations in the *thrC* gene and the *ilvA* gene capable of blocking synthesis of L-threonine and an adjacent pathway of L-threonine metabolism. (JX 1 at col. 10, lines 36-42) The resultant strain, VL334 (pYN7), is resistant against penicillin and capable of growing on a medium without amino acids. (JX 1 at col. 10, lines 43-48) In each cell, there are approximately twenty copies of the pYN7 plasmid. (JX 1 at col. 10, lines 49-51)

FN26. This conflicts with the information provided in the Russian priority patent, where the molecular weight of the plasmid pYN7 was set forth as 7.1 Md. (PX 2 at 92)

82. After constructing VL334 (pYN7), Genetika continued to conduct research aimed at constructing threonine-producing strains. By 1979, the Genetika inventors developed the bacterial strain M1 (pYN7). The inventors obtained U.S. Patent No. 4,321,325 ("the '325 patent") entitled "Process for Producing L-threonine," for the method of producing threonine using the M1 (pYN7) strain. (DX 61) M1 (pYN7) was not made by using the process claimed in the '765 patent. Rather, M1 (pYN7) was selected on the basis of the natural variability of VL334 (pYN7) by "being inoculated to an agar-doped culture medium." (DX 61 at col. 3, lines 14-17, 45-46) The strain M1 (pyN7) was isolated by selecting for colonies able "to produce L-threonine on a minimal glucose-salt nutrient medium and to retain the plasmid in the course of fermentation." (DX 61 at col. 3, lines 47-51) The location of the mutation, whether on the plasmid or on the chromosome and the specific gene affected, is unknown. (D.I. 308 at 274-76; D.I. 313 at 968-70) M1 (pYN7) differs from VL334 (pYN7) in, *inter alia,* having greater stability and an increased threonine-producing capacity (the average rate of accumulation of threonine by M1 (pYN7) being five times greater than that of VL334 (pYN7) and M1 (pYN7) producing 50% more threonine than did VL334 (pYN7)). (DX 61 at col. 4, lines 28-53; col 6, lines 28-31) It is undisputed that M1 (pYN7) and VL334 (pYN7) are different strains. (D .I. 308 at 319; D.I. 313 at 969-70)

***22** 83. The Genetika inventors continued their research using the M1 (pYN7) strain. In 1992, the inventors obtained U.S. Patent No. 5,175,107 ("the '107 patent"), entitled "Bacterial Strain of Escherichia Coli BKIIM B-3996 as the Producer of L-threonine." (DX 15) The '107 patent covers the bacterial strain of E. coli BKIIM B-3996 as the producer of L-threonine. In setting forth a method of constructing B-3996 from M1, the '107 patent made reference to an intermediate strain, G472T23. (DX 15 at col. 2, lines 26-31) G472T23 was made through a two-step process: (1) transduction of Ml by a bacteriophage bearing a determinant of saccharose assimilation, followed by (2) selection of spontaneously arisen mutants.

(DX 15 at col. 2, lines 14-26) The G472T23 (pYN7) strain was isolated as one of the mutant strains. G472T23 (pYN7) is described in the '107 patent as a spontaneously arising mutant variant of MI that is capable of "utilizing saccharose and saccharose-bearing substrates, such as molasses, as a source of carbon" and is resistant to both L-threonine and L-homoserine. (DX 15 at col. 4, lines 14-21, 29-31) The strain is auxotrophic for threonine, has a leaky mutation for isoleucine synthesis, and has an amplifiable plasmid containing a chromosomal fragment bearing the threonine operon. (D.I. 307 at 136) The strain also produces 53 g/l of threonine as compared to 20 g/l for VL334 (pYN7). (PX 977 at 26-27; JX 1 at col. 11, lines 50-61) It is undisputed that the strains G472T23 (pYN7) and M1 (pYN7) are different. (D.I. 308 at 319; D.I. 313 at 975)

I. Genetika's Assignment of the '765 Patent to Ajinomoto

84. The rights embodied in the '765 patent were granted to the fourteen named inventors pursuant to the laws of the United States. (PX 2 at 1) Plaintiff asserts that, because the invention was made by the inventors in the course of their employment at Genetika, an institution of the Soviet state, the rights in the '765 patent became the property of the Soviet state. (D.I. 196 at ex. 5 at ¶ ¶ 24, 26, 27, 40, 44, 62, 103, 108) Ajinomoto did not offer into evidence any assignments of the '765 patent from the named inventors to Genetika or any of its predecessors-in-interest.[FN27]

> FN27. A purported confirmatory assignment from the inventors to Ajinomoto (PX 385), which was filed in the PTO to protect Ajinomoto against subsequent assignments under 35 U.S.C. § 261, was on Ajinomoto's evidence list but was never offered into evidence.

85. On July 21 1982, Ajinomoto entered a license agreement with Licensintorg, the Soviet government's technology licensing entity, granting Ajinomoto the exclusive U.S. rights to the '765 patent. (PX 3; D.I. 311 at 668-69; D.I. 312 at 907-08) The agreement stated that "the Licensor[, Licensintorg,] is entitled by the Author[, Genetika,] to negotiate." (PX 3) Specifically, the agreement granted Ajinomoto the "exclusive right to use the ['765] patent, know-how, technical documentation and strain [G472T23 (pYN7)] for the production, use and/or sale of the licensed product[, L-threonine produced by the method employing G472T23 as developed by Genetika,] in Japan and the U.S. (PX 3 § 2.1(a)) Additionally, Ajinomoto received strain G472T23 (pYN7), which had been developed and was owned by Genetika. (PX 3 at 3538, 3562)

*23 86. In 1987, Licensintorg was succeeded by Medexport, another Soviet government agency. (D.I. 311 at 668-89; PX 6; PX 9)) All rights and obligations of Licensintorg under the license agreement were transferred to Medexport. (PX 10)

The license agreement was amended in both December 1989 and December 1990. (PX 6; PX 9) The latter addendum between Ajinomoto and Medexport granted Ajinomoto
an exclusive right to use the strain E. coli VNIIGenetika 4272T-23, PATENTS, TECHNICAL DOCUMENTATION and KNOW-HOW, concerning this strain to manufacture, use and sell the LICENSED PRODUCT on the base of this strain throughout the whole world except for the [U.S .S.R.], Czechoslovakia, Belgium, Denmark, Finland, Germany, Holland, Iceland, Luxemburg, Norway, Sweden.

(PX 9 § 2(c))

87. In January 1991, all rights and obligations of Medexport under the license agreement and addendums 1 and 2, including the '765 patent, were transferred from Medexport to Genetika, the legal successor of Medexport. (PX 15; D.I. 311 at 665-71; D.I. 312 at 907-08)

88. Effective May 14, 1991 Genetika assigned and transferred to Ajinomoto "all rights, title and interest" to the '765 patent. (JX 4) In August 1994 this agreement was amended to reflect a change in theroyalty payment. (JX 5)

89. In a memorandum to Genetika concerning the measures to be taken against ADM for alleged infringement, Ajinomoto stated that "there remains a succession certification procedure problem from Licensintorg." (DX 116 at AJ-FRFT008415)

J. Genetika's License of the Strain G472T23 (pYN7) to A.C. Biotechnics

90. **The License.** On or about September 9, 1986, Licensintorg granted a license to use G472T23 to A.C. Biotechnics, ABP International AB's ("ABP") predecessor. (JX 6) This agreement expressly granted ABP "the exclusive right to use the licensed strain, knowledge and patents for the purpose of manufacturing of L-threonine in the territory [-Belgium, Denmark, Finland, FRG, Holland, Iceland, Luxemburg, Norway, and Sweden-] and the non-exclusive right to use and sell

L-threonine, thus produced, in the territory and the zone of nonexclusive right[, worldwide but for the U.S.A. and Japan.]" (JX 6 § § 1.6, 1.5, 2.1) In addition the agreement granted ABP "the right to grant sub-licenses hereunder to third parties limited as said in article 2.1." (JX 6 § 2.4) ABP was required to keep Licensintorg informed of any sub-licenses and the rights assigned to the sublicensees. (JX 6 § 2.4) The agreement also provided that the parties were to "inform each other of all improvements and modifications," made to the licensed strain and that the "terms of transferring such improvements and modifications [were] to be agreed upon between the parties in each separate case," (JX 6 § § 8.1, 8.2).

91. **The Construction of ABP's Strain G472T23 (pYN8).** ABP constructed the strain G472T23 (pYN8) from G472T23 (pYN7), which it received from Genetika. ABP used the plasmid pYN7, which had an incomplete (i.e., defective) tetracycline resistant gene, from strain G472T23 in constructing the plasmid pYN8. According to expert testimony and the "owner's manual" [FN28] (PX 35), ABP isolated the plasmid pYN7 and cut it using restriction endonucleases so as to isolate the chromosomal DNA fragment containing the threonine operon. (D.I. 307 at 165-66; D.I. 313 at 978079) The remaining plasmid DNA, an incomplete copy of pBR322, was removed and discarded and thus was not used to form pYN8. (D.I. 307 at 165-66)

FN28. The manual was provided to ADM by ABP when it purchased the strain.

***24** 92. According to the genealogy set forth in the record, the feedback resistant threonine operon (mutation in *thrA*) in pYN7 was chromosomal DNA obtained from donor strain MG442. (PX 35 at 2393; PX 966 at 36; D.I. 307 at 126-131) ADM contests this assertion, arguing that the evidence indicates that the descendant pYN7 plasmid differs genetically and structurally from the original pYN7 plasmid and thus the chromosomal fragment found in pYN8 is neither structurally or genetically the same fragment initially isolated from the donor bacterial chromosome. (D.I. 325 at 25-26)

It is undisputed that the strains M1 (pYN7) and G472T23 (pYN7) were not constructed using the method set forth in the '765 patent, but were the result of spontaneously occurring mutations, the number and location of which were unknown. It is also undisputed that each subsequent strain was improved in its ability to produce threonine over the parent strain from which it was derived. Although the plasmid maps depicting the pYN7 plasmid in the '765 patent (JX 1 at Fig. 5), the Russian priority document (PX 2 at 56), the '107 patent (DX 15) and the ABP manual (PX 35 at 2390) all vary with respect to the size of the plasmid in terms of megadaltons or kilobases, the maps are the same in terms of the restriction sites. (D.I. 308 at 294) Moreover, the maps do not indicate any change in the structure of the threonine operon or its origin. In fact, in its submission to the Japanese Ministry of Agriculture, Forestry and Fisheries, ADM represented that the threonine operon in pYN8 was "E. coli chromosome fragments" that were derived from the donor strain MG442. (PX 321 at 2754-55)

93. It is undisputed that the *asd* gene, which catalyzes the second step of threonine synthesis, was not present on the chromosomal fragment used by ABP to construct pYN8. (D.I. 307 at 137-38, 140, 156-57, 159, 161; D.I. 308 at 186, 187-89, 322-24; D.I. 313 at 979-80, 986-87, 943-44)

94. The isolated chromosome fragment from pYN7 was then ligated with plasmid DNA (pBR322) bearing a replacement tetracycline resistant gene and a spacer DNA fragment from plasmid pSGS18. (PX 35 at 2391, 2394; PX 63 at 1655; DX 498) The resultant hybrid plasmid, pYN8, contained an operating ampicillin resistant gene, an operating tetracycline resistant gene, and spacer DNA; the latter two items not being found in pYN7. (PX 35 at 2394; PX 977 at 25) Plasmid pYN8 had a length of 11.5 kilobases (kB), (PX 35 at 2391), as compared to pYN7 which had a length of 10.4 kB, (PX 35 at 2390).

95. The hybrid plasmid, pYN8, was used to transform the host strain, G472T23. According to the ABP manual, plaintiff's expert, and the genealogy presented in the record, G472T23 was a mutant strain of E. coli K-12 that was auxotrophic for threonine by a mutation in the *thrC* gene and was partially blocked in threonine metabolism by a mutation in the *ilVA* gene. (PX 35 at 2393, 2396-97; PX 966 at 28-29, 31; D.I. 307 at 151-156) The resultant strain, G472T23 (pYN8), possessed an increased productivity of threonine, producing 80-90 g/l of threonine versus 53 g/l for G472T23 (pYN7) and 20 g/l for VL334 (pYN7). (JX 1 at col. 11, lines 50-61; PX 966 at 31; PX 977 at 26-28; D.I. 308 at 217, 221; D.I. 307 at 158-60, 162; D.I. 314 at 1128-29, 1145, 1150)

***25** 96. ADM contends that the strains it obtained from ABP do not have the *ilvA* leaky mutation as evidenced by the fact that, in order to maximize threonine production, ADM has added isoleucine in one form or another to its threonine seed fermenters since it began the commercial production of threonine. (D.I. 316 at 1472-74) According to the ABP manual, however, the fact that G472T23 has the leaky *ilvA* gene decreases the strain's ability to produce isoleucine and, therefore, there is a need for an addition of isoleucine. (PX 35 at 2396-97) In addition, Mr. Steven F. Stoddard, a group leader in ADM's